UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/184,572	11/02/1998	LISA MCKERRACHER	99999/MARUSY	4396

26211 7590 05/02/2006

FISH & RICHARDSON P.C.
P.O. BOX 1022
MINNEAPOLIS, MN 55440-1022

EXAMINER	
TURNER, SHARON L	
ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 05/02/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/184,572	MCKERRACHER ET AL.	
	Examiner	Art Unit	
	Sharon L. Turner	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 January 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25-29,43 and 45-47* is/are pending in the application.

4a) Of the above claim(s) *25-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *43 and 45-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *25-29,43 and 45-47* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 6403, 4-3-06
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Response to Amendment

1. The amendment filed 1-17-06 has been entered into the record and has been fully considered.

2. The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

3. As a result of applicant's amendment, all rejections not reiterated herein have been withdrawn.

4. Claims 25-29, 43 and 45-47 are pending.

5. Claims 25-29 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 10.

Priority

6. Reconsideration of the priority determination with respect to the newly amended claims and Applicants arguments is considered persuasive to provide benefit to the 10-31-97 date as supported within the 2,214,841 application.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 43 and 45-47 are rejected under 35 U.S.C. 103(a) as being unpatentable

over Kamata et al., Microbiol., Immunol., 38(6):421-428, 1994, Johnson et al., US Patent No. 5,851,786 issued 12-22-98, filed 9-27-95, Varon et al., J. of Neurotrauma 11(5):473-486, 1994, Mobley et al., 5,134,121 July 28, 1992, Mattson et al., Stroke 1993, 24(12):I136-40; discussion I144-5, Olson et al., J. of Neurol., 1994 Dec., 242 (1Suppl. 1):S12-15 and Olson et al., Acta Neurochirurgica Supplementum, 1993, 58(3-7).

Kamata et al., teach chick dorsal root ganglia (DRG) induced nerve outgrowth via administration of C botulinum C3 exoenzyme (ADP-ribosyltransferase) that is at least as effective as DRG outgrowth induced via the neurotropic factor NGF, a noted neurotrophic factor recognized as being effective in in vitro and in vivo use for stimulating neurite outgrowth both within CNS and PNS and within neuronal or spinal cord injury including following surgery, see in particular abstract, Effects of C3 exoenzyme on the morphology of cultured cells, pp. 424-425 pp. 427, lines 2-23. Based on such evidence Kamata et al., conclude that C3 exoenzyme is a neurotropic agent. DRG cells contain both central and peripheral projections and thus the outgrowth is of CNS although the outgrowth is in culture.

Johnson et al., teach a method of treating an individual to regulate actin polymerization, stress fiber formation and/or focal adhesion assembly by administration of a compound such as Botulinum C3 exoenzyme also known as ADP-ribosyl C3 transferase at 100ng/ul, see in particular column 14, line 56-line 15, line 59, column 18, lines 30-63 and Example 3, including administration directly to a cell in vivo, ex vivo or systemically, see in particular column 18, line 44. Additionally administration is as in

column 15-16 including subcutaneous, intramuscular or transdermal. The administration may be measured functionally including detecting neuronal response and for a therapeutic composition for the treatment of Parkinson's or Alzheimer's disease, see in particular Abstract and column 17, lines 18-58 and claim 40. As the administration routes are systemic the administration necessarily results in the administration at sites of lesion including to neurons within the PNS and CNS. It is further noted that the method is effective to treat Alzheimer's and Parkinson's disease which are recognized as affecting CNS brains neuronal cells which exhibit focal lesions.

Kamata et al., et al., teaches that C3 ADP-ribosyl transferase acts as a neurotrophic factor to PNS and CNS cells (DRG ganglia) in vitro, similar to nerve growth factor. Johnson et al., teaches administration of C3 ADP-ribosyl transferase to patients for treatment of neurological disorders with notable effects being equated to regeneration or the re-establishment of functional connections and repair of damaged neuronal cell pathways.

Kamata et al., and Johnson et al., and fail to teach in vivo administration of C3 exoenzyme via infusion into a site of surgery for spinal cord lesion to increase neurite regeneration in spinal cord lesion following damage and to promote regeneration and neuronal outgrowth within the CNS in a patient.

Varon et al., teach that neurotrophic factors are well recognized for their important function on developing neurons of the PNS, to prevent or reduce degenerative responses of adult CNS to a variety of diseases and injuries, and in the regeneration of adult CNS in animals. Varon et al., further teach various model systems

utilizing in vivo administration of NGF to promote neuronal outgrowth in the CNS in vivo. NGF is a molecule that has been isolated as a neurotophic factor based upon it's ability to promote neurite outgrowth in dorsal root ganglia assays including following surgery or operation.

Mobley et al., similarly teach NGF and NGF variants that are useful in the treatment of multiple neurological diseases via the mechanism of promoting neurite outgrowth, see in particular columns 6-7 and 16-18. Mobley et al., further teach that a suitable assay to screen for such molecules is via assessing the ability of a molecule to promote neuronal outgrowth in cultured dorsal root ganglia cultures, see Bioassay with dorsal root ganglia neurons, columns 19-20.

Mattson et al., teach protection of CNS neurons in culture from neuronal damage and death in a stroke model via treatment with nerve growth factor including after surgery or operation.

Olson et al., 1993 and Olson et al., 1994 teach the similarity in protection via nerve growth factor administration amongst different CNS model systems and predict its general applicability not only in the neurodegenerative diseases but for treatment of ischemia, stroke and injury, including treatment after surgery or operation, see in particular abstract.

Thus, Mobley et al., and Varon et al., Mattson et al., Olson et al., 1993 and Olson et al., 1994 teach the recognition in the art of neurotrophic factors to promote axon outgrowth in the CNS for a wide variety of diseases via mechanical introduction in patients, including for the stimulation of regeneration in treatments following surgery or

operation. Mobley et al., further evidences that a suitable assay for predicting such effects is the dorsal root ganglia assay that was originally used in the characterization of NGF and now a multitude of known neurotrophic factors that are effective both in vitro and in vivo to promote neurite outgrowth within the PNS and the CNS in patients. Thus, one of skill in the art would have been motivated based on Kamata and Johnson's teachings of C3 exoenzyme as a neurotrophic factor capable of stimulating CNS neuronal outgrowth in dorsal root ganglia cultures to use the same molecule to produces such effects in vivo in a patient in need of CNS axon outgrowth, including following operation or surgery as in spinal cord damage or transaction models. One of skill in the art would have expected success using such a method based on C3 exoenzyme's activity in promoting CNS axon outgrowth from DRG neurons in vitro and the art's teachings of such assays in predicting utility in promoting neurite outgrowth in the CNS of patients and the known art accepted models for establishing regeneration of axon outgrowth following surgery or operation as in regenerative models following spinal cord lesion. Thus, the cumulative reference teachings render the invention obvious to the skilled artisan. Applicant's comments with respect to the priority determination are particularly noted as it has been their position that the in vitro findings within the priority document combined with the prior art are sufficient basis for the artisan to be motivated to provide and expect success in in vivo treatments for the promotion of CNS neurite regeneration.

Applicants argue in the 1-17-06 response that Kamata does not disclose or suggest "C3ART"'s use in clinical application, or to site of surgery for lesion and lacks

motivation therefore. Applicants further argue that the '786 patent are not directed to the same activity as claimed and attempt to distinguish via mechanistic recitations a difference between inhibiting unwanted activity vs. enhancing neuronal outgrowth. Applicants also argue that the Varon, Mattson and Olson '92 and '93 references are on point to NGF and that in contrast C3ART is not associated to binding to receptors but inhibit Rho, a nerve growth inhibitor and accordingly motivation and expectation of success are lacking. Applicant further argues that Varon does not supplement as a bridge is not required, that Mattson is on point to "protection" and not enhancing axon outgrowth, that Olson is on point to brain and not traumatic spinal cord lesion and conclude that no proper motivation or suggestion is provided. Applicants argue that the references combined are not on point to site of surgery for traumatic spinal cord lesion and assert that the results are surprising and unexpected.

Applicants arguments filed 1-17-06 have been fully considered but are not persuasive. It is not necessary that Kamata teach all element of the claims, if so the reference would have been cited under the 102 statute. However, it is relevant that Kamata teches C3ART as a neurotropic agent and particularly one at least as effective as NGF, the art recognized standard for promoting neurite outgrowth in vitro and in vivo, including in spinal cord lesion due to surgery, see also Varon in a regrowth model following transaction (due to surgery) in dorsal spinal cord, particular abstract and NGF and the Spinal Cord Sensory Regeneration model pp. 474-478, directily on point to spinal cord injury as a result of axotomy within the spinal cord. Accordingly, the references are particularly on point. Applicants attempt to distinguish the '786 patent

via mechanistic recitations is also non-persuasive. Regardless, mechanistic recitations cannot counter the direct administration that is the same. The '786 teaches administration of C3ART to the patient populations exhibiting neurological/neurodegenerative disorder. The following excerpt evidence that the '786 patent is on point, even to spinal cord injury and further to surgical injury of CNS which is reasonably inclusive of spinal cord which is a recognized part of the CNS, having both peripheral and central components. Similarly, note that NGF is recognized similarly in Varon for axonal repair in such central injury disorders and Parkinsons and Alzheimers were outgrowth is recognized therefrom in response to neurotropic factors.

Detailed Description Text (61):
"Neurodegenerative disorder " is defined herein as a disorder in which progressive loss of neurons occurs either in the peripheral nervous system or in the central nervous system. Examples of neurodegenerative disorders include: (i) chronic neurodegenerative diseases such as familial and sporadic amyotrophic lateral sclerosis (FALS and ALS, respectively), familial and sporadic Parkinson's disease, Huntington's disease, familial and sporadic Alzheimer's disease, multiple sclerosis, olivopontocerebellar atrophy, multiple system atrophy, progressive supranuclear palsy, diffuse Lewy body disease, corticodentatonigral degeneration, progressive familial myoclonic epilepsy, strionigral degeneration, torsion dystonia, familial tremor, Down's Syndrome, Gilles de la Tourette syndrome, Hallervorden-Spatz disease, diabetic peripheral neuropathy, dementia pugilistica, AIDS Dementia, age related dementia, age associated memory impairment, and amyloidosis-related neurodegenerative diseases such as those caused by the prion protein (PrP) which is associated with transmissible spongiform encephalopathy (Creutzfeldt-Jakob disease, Gerstmann-Straussler-Scheinker syndrome, scrapie, and kuru), and those caused by excess cystatin C accumulation (hereditary cystatin C angiopathy); and (ii) acute neurodegenerative disorders such as traumatic brain injury (e.g., surgery-related brain injury), cerebral edema, peripheral nerve damage, spinal cord injury, Leigh's disease, Guillain-Barre syndrome, lysosomal storage disorders such as lipofuscinosis, Alper's disease, vertigo as result of CNS degeneration; pathologies arising with chronic alcohol or drug abuse including, for example, the degeneration of neurons in locus coeruleus and cerebellum; pathologies arising with aging including degeneration of cerebellar neurons and cortical neurons leading to cognitive and motor impairments; and pathologies arising with chronic amphetamine abuse including degeneration of basal ganglia neurons leading to motor impairments; pathological changes resulting from focal trauma such as stroke, focal ischemia, vascular insufficiency, hypoxic-ischemic encephalopathy, hyperglycemia, hypoglycemia or direct trauma; pathologies arising as a negative side-effect of therapeutic drugs and treatments (e.g., degeneration of cingulate and entorhinal cortex neurons in response to anticonvulsant doses of antagonists of the NMDA class of glutamate receptor). and Wemicke-Korsakoff's related dementia. Neurodegenerative diseases affecting sensory neurons include Friedreich's ataxia, diabetes, peripheral neuropathy, and retinal neuronal degeneration. Neurodegenerative diseases of limbic and cortical systems include cerebral amyloidosis, Pick's atrophy, and Retts syndrome. The foregoing examples are not meant

to be comprehensive but serve merely as an illustration of the term "neurodegenerative disorder."

Accordingly, the '786 patent is not distinguished via mechanism, where the same administration of the same compounds for the same purposes is suggested. Similarly, same mechanism is not required. Kamata places C3ART in the art as a neurotropic factor. Its use therefore may similarly be suggested by widely art accepted knowledge at the time of the invention for administration at sites, locales and for purposes of benefit in axon outgrowth, regeneration and restoration of functioning nerves. The art motivates the artisan to use neurotrophic factors in this way and the art further evidences success. Varon remains on point as a bridge is neither expressly included or excluded. This is an art accepted model system and the teachings are not limiting. Matson's "protection" is synonymous with survival and maintenance of neuronal connections. The "traumatic" event of the claims involves surgery but it does not preclude that excitotoxic and/or ischemic events occur in response to lesion insult. NGF recognized repair therefore is on point to CNS survival in the patient and relevant. Nevertheless Matson is on point and was cited for the further recognition of neurotrophic factor benefits in mechanical lesion models, see in particular in axotomy damage as cited at p. 136 column 1, and suggestion for CSF administration as at p. 139 column 1 of Matson. Similarly, Olson is on point to NGF neurotrophic factor benefits in mechanical lesions in CNS, even if not of spinal cord surgery specifically. Accordingly, the cumulative references indeed support the widely art accepted and evidenced principle that neurotrophic factors are beneficial in promoting axon outgrowth within the CNS, in response to lesion, and in spinal cord lesion specifically. Accordingly the

cumulative references do render the invention obvious and motivate the artisan to administer C3ART neurotrophic factor for such purposes. The cumulative references further evidence an art expectation of success and therefore the invention is not unexpected or surprising. No further evidence of unexpected or surprising findings is shown consistent with MPEP 716.02 requirements. No comparison is provided. Accordingly rejection is maintained.

Status of Claims

9. No claims are allowed.

Conclusion

10. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

11. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon L. Turner, Ph.D. whose telephone number is (571) 272-0894. The examiner can normally be reached on Monday-Thursday from 7:00 AM to 5:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached at (571) 272-0867.

Sharon L. Turner, Ph.D.
March 30, 2006